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CHRONIC KIDNEY DISEASE: ON THE WAY TO CONCEPTUAL UNITY

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The development of a convenient, rational and theoretically sound classification of chronic kidney disease (CKD) remains one of the most challenging problems in contemporary nephrology. At present, the number of patients suffering from chronic renal pathologies is rapidly increasing all around the world. Such factors as population ageing and increased prevalence of diabetes have resulted in a steep rise in the incidence of renal disorders of a vascular nature [19]. In addition, views on the development and progression of CKD have been fundamentally transformed over the last decades [2]. Thus, a widely-held belief that the progression of CKD leading to terminal chronic renal failure should not be impeded has been challenged. It was earlier assumed that the disease would eventually require renal replacement therapy (RRT). In a sense, such an approach was leading the discipline of nephrology towards a dead end. Meanwhile, the number of patients with end-stage renal disease (ESRD) was growing explosively, leading to an increased demand for dialysis facilities and organ transplants. The costs of providing dialysis services were also increasing exponentially. As a case in point, the number of patients receiving RRT has recently achieved a total level of 1,400 people per 1,000,000 population in the US and Japan. [19]. Consequently, the associated management and funding issues have become increasingly pressing even for economically developed and wealthy countries.

On the other hand, recent advancements in the elucidation of pathological mechanisms driving CKD progression, as well as the identification of CKD risk factors have allowed the development of reasonably valid regimens of conservative therapy that have proven to be effective for controlling the disease course, postponing RRT and decreasing the number of fatal complications [11, 13-15, 17, 18, 20, 22]. These achievements encouraged nephrologists to search for new guiding principles to inform the selection of appropriate therapeutic strategies for particular clinical cases, depending on the stage of progression of the disease. Such a differentiated approach required risk factors in the development and progression of pathological processes in renal tissue to be determined. Only by considering risk factors, assessing their significance and ensuring the possibility of controlling a particular determinant (its modifiability), can the primary and secondary CKD prevention measures be effectively implemented.

All this required the creation of a common lexicon (if not a unified language) or an 'encyclopaedic dictionary of medical terms', which would provide clinical nephrologists with the commonly shared interpretations of basic concepts. As surprising as it might seem, until recently not only has there been no generally accepted classification for the various stages of the pathological renal process leading to impaired kidney function, but there has also been a lack of consistent terminology across the discipline. Moreover, it is fair to say that even today there is still no unity concerning the concept of chronic renal failure (CRF) among nephrologists both in Russia and abroad.

In any case, the issue of determining criteria against which clinicians could assess the severity of kidney disease, its prognosis, as well as the necessity and feasibility of using certain therapeutic approaches at various disease stages remained highly topical. It goes without saying that leading nephrologists were not able to ignore the problem: however, surprisingly, there were relatively few attempts to solve it. The first serious breakthrough in this direction was undertaken by D.E. Oken, who classified criteria for assessing the severity of a diagnosed kidney disease in 1970 [21]. Oken's classification comprised three principal categories: classification of symptoms (clinical manifestations), classification of the functional state of the kidneys, classification of the clinical state of the patient. Each category was divided into classes, with a class in one category corresponding to the respective class in another category. The criteria proposed by D.E. Oken also assumed the possibility of describing the severity of the patient's condition in a brief form, as a set of letters and numbers.

In our opinion, Oken's ideas had in many ways anticipated principles that were later to be embedded in numerous widely-accepted classifications describing not only kidney disorders, but also some other internal diseases. One of such examples is the classification of heart failure adopted by the New York Heart Association [1]. Despite its significant contribution, Oken's classification has not to the best of our knowledge been used in its pure form. The reason for that may be a certain cumbersomeness and respective practical inconveniences in using this scheme [5]. However, we believe that the main obstacle to the widespread dissemination of Oken's principles for assessing the severity of renal pathology was the inability of nephrologists at that time to adopt what might have seemed in many respects a revolutionary approach.

Russian nephrologists were not exempted from efforts to create a classification for assessing the severity of the condition of patients suffering from chronic kidney disease. As far as we are concerned, the most successful attempts in this direction were carried out by S.I. Ryabov and B.B. Bondarenko [5], who proposed a classification of chronic renal failure. In fact, their scheme reproduced a somewhat modified and supplemented category "classification of the functional state of the kidneys" from Oken's classification. Later on, S.I. Ryabov introduced several modifications into the initial scheme (Table 1) [3, 4, 6].

The classification proposed by S.I. Ryabov and B.B. Bondarenko distinguished three stages – or degrees – of chronic renal failure (CRF). It should be noted that the authors alternatively use the terms 'stage' and 'degree' in their different publications, without giving a clear definition of either concept. Each of the aforementioned stages was divided into two phases – A and B. This classification gave physicians guidance for the management of patients with CRF. A particularly useful was a category designated as a 'group'. Group '0' implied treatment of the main condition; group '1' – prescription of a low-protein diet and conservative therapy; group '2' – prescription of hemodialysis, RRT; group '3' – use of conservative therapy [4].

Ryabov and Bondarenko's classification (as any classification, in principle) contained a number of internal contradictions and even some erroneous statements. Honestly speaking, the latter can be regarded as errors only from the perspective of contemporary views on the development and progression of pathological renal processes and recent achievements in the field of kidney disease therapy. In any case, this classification has played an extremely positive role as it was being successfully used across the entire USSR territory, e.g. in St. Petersburg and many regions of the North-West of Russia. Sadly, the classification has not received the public and official recognition it deserves. Russian specialists were authors of a number of other CKD classification schemes. Some of them now have a purely historical significance or have received even less recognition than Ryabov and Bondarenko's classification, while others pursued highly-specialized goals (medical and social expertise, transplantology, renal failure in urological diseases).

All in all, at that time the discipline was lacking a generally accepted and convenient classification of chronic kidney diseases that would have met the high standards of (then) contemporary nephrology. This produced a paradoxical situation, since many internationally recognized guidelines on nephrology either sidestepped the questions of CKD classification, or gave rather unclear interpretations. All this was fully applicable to the "bible" of nephrology, a manual

Table 1

Classification of Chronic Renal Failure (CRF)
(S.I. Ryabov [3])

Stage	Phase	Name	Laboratory criteria		Form	Group	Indicators insignificantly dependent of CRF severity
			Creatinine, mmol/L	Filtration rate			
I	A	Latent	up to 0.13	up to 50% from the norm	Reversible	0	Biochemical: urea, residual nitrogen, electrolytes, acid-base balance Clinical: arterial pressure (AP), anemia
	B					0	
II	A	Azotemic	0.13–0.44	20–50% from the norm	Stable	1	
	B		0.45–0.71	10–20% from the norm	Progressing		
III	A	Uremic	0.72–1.24	5-10% from the norm		2	
	B		1.25 and over	Less than 5% from the norm		2, 3	

Table 2

Criteria of Chronic Kidney Disease

Criterion	Description
1.	Renal injury with a duration of ≥3 months, which is manifested as functional or structural alterations in the activity of the organ followed by increased or unchanged GFR. The condition is manifested in: -pathological and morphological alterations in the kidney tissue -shifts in blood and urine composition, as well as alterations observed using the methods of renal structure visualization
2.	GFR level <60 mL/min/1.73 m^2 during the period of three or more months, under the presence or absence of other renal injury signs

Note: GFR - Glomerular filtration rate

edited by B.M. Brenner [10]. The situation was becoming more and more desperate when, finally, the National Kidney Foundation (NKF, USA), took up the challenge. A large group of experts took part in the development a classification, including specialists in nephrology, paediatric nephrology, epidemiology, clinical laboratory diagnostics, dietology, social activity, gerontology and family medicine. As a result of the analysis of numerous publications on the diagnosis and treatment of kidney disease, assessment of various indicators depicting the rate of kidney disease progression, clarification of terminological concepts, consultations with the representatives of medical administrative bodies, a consensus was reached. The definition of *chronic kidney disease* (CKD) was formulated based on a series of criteria (Table 2) [9]. Since then, CKD has been defined as "the presence of kidney injury or a decrease in the level of kidney function during three or more months, regardless of the diagnosis" [9].

The independence of CKD from the main condition is the most important principle in the diagnostics of this disease. Nevertheless, CKD does not dispense with a nosological approach to diagnosing a particular kidney disease that has caused CKD; in some cases, it even emphasizes its significance. This idea is confirmed, e.g., by the fact that the NKF recommended the introduction of a separate standard for managing patients with diabetic nephropathy [9], largely because this pathology requires a strict control of glycaemia. Only under this condition can the desired therapeutic effect from interventions aimed at reducing the rate of renal function deterioration be achieved (angiotensin-I-convertase inhibitors, angiotesin II (AT_1) receptor blockers, non-dihydropyridine calcium-channel blockers, low-protein diet).

NKF experts also proposed a CKD classification that singles out five stages of the disease, depending on the severity of kidney function deterioration (Table 3). An important feature in this classification is the differentiation of risk factors in the CKD development and progression (Table 3), which is considered to be one of the most important achievements in contemporary nephrology [19].

A careful analysis of literature sources allowed one of us [7] to identify a number of situations, in which the acceleration of CKD progression or an increase in the probability of CKD development (Figure 1) can be expected. It should be emphasized that the effect of some risk factors can be eliminated or, at least, reduced (modifiable factors), while the effect of others cannot be mitigated at all. Nevertheless, non-modifiable risk factors should be considered when assessing the severity of a patient's condition and CKD prognosis.

Generally speaking, the question of CKD risk factors is not that straightforward. The problem is that one and the same circumstance can act as a risk factor both in the CKD development and the progression of an already existing kidney dysfunction. This fact also drew the attention of NKF experts, who noted that a high level of blood pressure can be simultaneously both a cause and a complication of CKD. At the same time, it was shown that increased systemic arterial pressure quite often determines not only the rate of CKD progression, but also a greater probability of the development of various cardiovascular complications [9].

As can be seen from Table 3, a CKD stage (severity) in the NKF classification is estimated according to the magnitude of glomerular filtration rate (GFR) reduction. NKF experts rightly considered GFR to be convenient for assessing the functional state of the kidneys, since this parameter is clear and easy for physicians of almost all specialities to apply. In addition, having comprehensively studied publications examining correlations between GFR and CKD manifestations and complications, the authors of the NKF report proposed a scientifically credible scale for assessing CKD severity. GFR is supposed to be measured using the simplest methods based on a single measurement of serum creatinine. It is considered reasonable to apply the Cockcroft and Gault formula [12] or MDRD (Modification of Diet in Renal Dis-

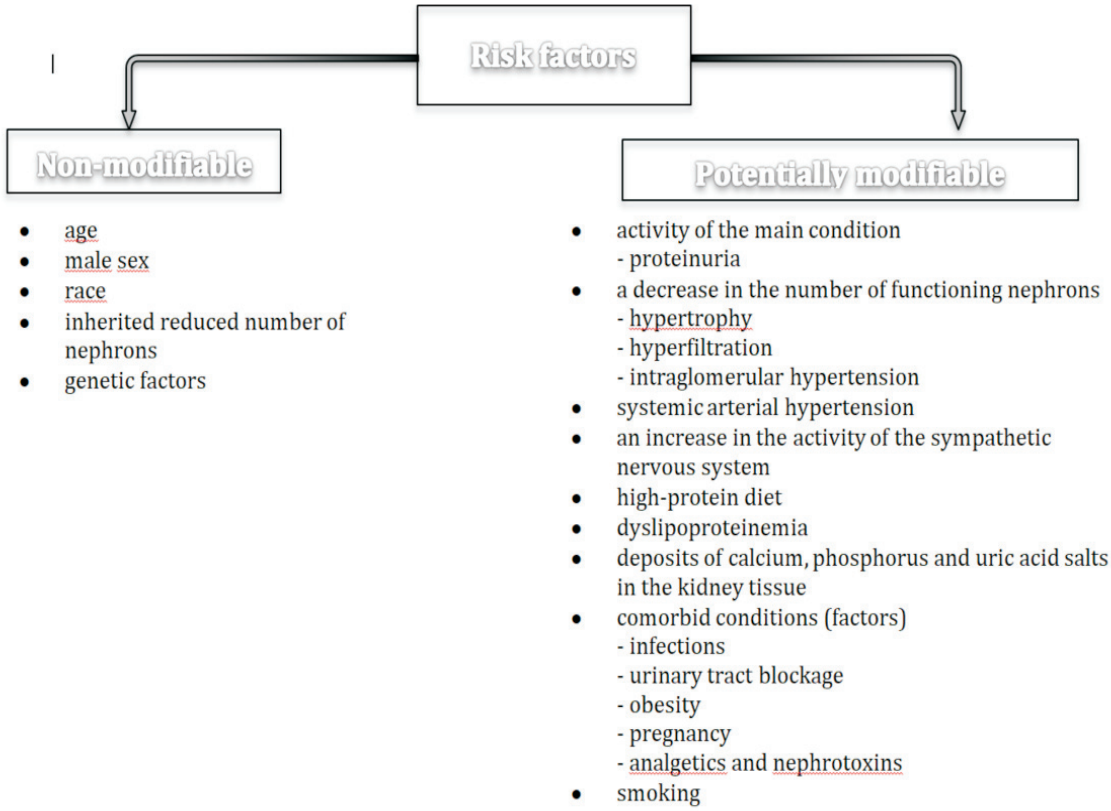

Figure 1. Risk factors in the progressing of Chronic Kidney Disease

ease) equations derived in the course of a multicentre controlled trial [16], which permit an estimation of the creatinine clearance level based on creatinine concentration in the blood serum, such parameters as age, sex, race, height and body weight, as well as a number of other readily available laboratory indicators.

We believe that the concept of CKD is very close to definitions broadly accepted in cardiology, i.e. Ischemic Heart Disease (IHD) and Chronic Obstructive Pulmonary Disease (COPD). It seems likely that the creators of the CKD concept were – whether consciously or unconsciously – guided by IHD notions. Indeed, in our opinion, there is much in common between the conditions of CKD and IHD (Table 4).

A number of analogies can also be identified between such pathomorphological and pathophysiological processes as atherosclerosis and glomerulosclerosis, which result respectively either in IHD or CKD (Table 5). Indeed, the development of atherosclerotic vascular damage to a great extent depends on impaired lipid metabolism that forms a basis for lipid infiltration into the blood vessel walls. On the other hand, manifestations of dyslipoproteinemia are also very common in most kidney disorders. It should be mentioned that various kinds of hyperlipidemia are

Table 3

Classification of Chronic Kidney Disease (NKF, USA)

Stage	Characteristics	GFR level (mL/min/1.73 m^2)	Recommended measures
	Presence of risk factors:	≥ 90	Supervision, measures aimed at decreasing the risk of renal pathology development
I	Renal injury with a normal or increased GFR	≥ 90	Diagnostics and treatment of the main condition aimed at reducing its progression rate and decreasing the risk of cardiovascular complications
II	Renal injury with a modest GFR reduction	60-89	Assessment of the disease progression rate
III	Renal injury with a medium GFR reduction	30-59	Identification and treatment of complications
VI	Renal injury with a pronounced GFR reduction	15-29	Preparation to renal replacement therapy
V	End-Stage Kidney Disease	<15 or admission of dialysis	Renal replacement therapy (in case of complications)

Table 4

Analogies between the concepts of Chronic Kidney Disease (CKD) and Ischemic Heart Disease (IHD)

IHD	CKD
Death of a part of myocytes	Death of a part of nephrons
Presence of heart remodelling (hypertrophy of undamaged myocardium parts)	Hypertrophy of undamaged nephrons
Substitution of died myocytes with connective tissue	Substitution of a part of nephrons with connective tissue
A decrease in the organ functioning	A decrease in the organ functioning
One of the main therapeutic approaches is cardio-protection	One of the main therapeutic approaches is nephro-protection (reduction of increased systemic arterial pressure, low-protein diet, angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotesin II (AT_1) receptor blockers, non-dihydropyridine calcium-channel blockers)
Outcome – heart failure	Outcome – kidney failure
Ultimate effective treatment approach – heart transplantation	Ultimate effective treatment approach – kidney transplantation
Overlapping of multiple IHD and CKD risk factors	Overlapping of multiple CKD and IHD risk factors

almost always observed in nephrotic syndrome, diabetic nephropathy or under a pronounced decrease in kidney function.

The list of analogies between glomerulo- and atherosclerosis could be continued, e.g., by including their similar features in the formation of atherosclerotic vascular lesions and the development of tubulo-interstitial sclerotic alterations. However, the presented evidence is sufficient to conclude that the concept of CKD cannot be limited to a purely formal set of certain features; rather, the condition has a clear pathogenetic basis. This is also confirmed by the presence of a single mechanism driving the progression of various chronic kidney diseases, which initially leads to a reduction in the mass of functioning parenchyma and, subsequently, to the development of hyperperfusion, hyperfiltration, and intraglomerular hypertension in surviving glomeruli [2].

Nonetheless, there are still many issues associated with the introduction of the CKD concept in the practice of Russian medicine. One of these, although purely formal, is nevertheless significant for both nephrologists, general practitioners and specialists in the field of medical and social expertise: *how should a diagnosis be formulated using the concept and stages of CKD?* The authors of the NKF report partially answered this question. According to their recommendations, a patient with CKD should be evaluated in a number of ways. Account should be taken of the main diagnosis, comorbid disorders, degree of renal dysfunction (on which the severity of the patient's condition depends), complications associated with the degree of kidney function impairment, presence or absence of risk factors contributing to further deterioration in the functional state of the kidneys and various cardiovascular disorders. This approach is entirely consistent with the practice of formulating a highly-detailed diagnosis, which is deeply embedded in Russian medical tradition.

Let us consider, for instance, the case of a patient with membranoproliferative glomerulonephritis, a

Table 5

Analogies between the formation of glomerulo- and atherosclerosis

Atherosclerosis	**Glomerulosclerosis**
Dyslipoproteinemia	Frequent dyslipoproteinemia associated with kidney diseases
Systemic hypertension	Glomerular hypertension and (or) transmission of increased blood pressure into the vascular system of glomeruli
Slowing the progression of atherosclerosis by admission of hypolipidemic agents	Slowing the progression of glomerulosclerosis (at least in experiments) by admission of hypolipidemic agents
Hypercellularity (proliferation of smooth muscle cells)	Hypercellularity (proliferation of mesangial cells)
Increased content of extracellular collagen, elastin and proteoglycans	Increased content of the mesangial matrix
Infiltration of atherosclerotic lesion sites with macrophages followed by the formation of foam cells	Frequent identification of foam cells in glomerulosclerosis sites, particularly in nephrotic syndrome
Alteration in blood coagulation with a tendency to hypercoagulation	Alteration in blood coagulation with a tendency to hypercoagulation

slightly increased serum creatinine (serum creatinine concentration of 0.21 mmol/l), nephrotic syndrome and a slightly increased serum potassium concentration (e.g., serum potassium level of 5.7 mmol/l), who receives the following diagnosis:

CKD: Stage III, membranoproliferative glomerulonephritis, nephrotic syndrome, initial azotemia, anaemia, dyselectrolytemia

Considering that the intravital morphological examination of the kidneys is very rarely performed in Russian medical institutions, the abovementioned diagnosis should be re-formulated as follows:

CKD: Stage III, glomerulonephritis, nephrotic syndrome, initial azotemia, anaemia, dyselectrolytemia

It should be mentioned that glomerulonephritis is used without the adjective 'chronic' in this formulation. The very definition of CKD, if it is introduced into the diagnosis, presupposes the presence of a *chronic* kidney disease. On the one hand, in the case of acute glomerulonephritis, which can be resolved, the diagnosis of CKD is incorrect. On the other hand, if the course of acute glomerulonephritis has been protracted, the initial diagnosis of CKD can be removed in the future. Another question is whether the specialists of medical and social expertise departments can be satisfied with such a diagnosis when taking decisions about a person's fitness for military service or provision of a disability pension. The problem is that the diagnosis formulations given above lack the term 'chronic renal failure', on which experts from different medical administration bodies rely in the process of decision making.

In general, the concept of CKD does not exclude the term 'renal failure' (see Table 2), although the latter has slightly different meanings in Russia and abroad. In fact, the concept of 'renal failure' in the CKD classification corresponds to end-stage kidney disease or III-stage chronic renal failure in Ryabov and Bondarenko's classification (see Table 1). Therefore, following the logic of the CKD classification compilers, the diagnosis from the above case can be formulated as follows:

CKD, stage V (renal failure): Diabetes mellitus, type 1 (insulin-dependent), diabetic nephropathy, stage V, azotemia, acidosis, dyselectrolytemia

It should be mentioned that the idea of reconsidering notions about chronic renal failure conventional for many Russian specialists has long been in the air. To our knowledge, G.D. Shostka et al. were among the first Russian nephrologists to pay attention to this problem [8]. They rightly noted that "all the measures aimed at rehabilitation and social protection of patients with chronic renal failure are currently implemented only on the basis of the chosen treatment tactics (conservative therapy, hemodialysis, peritoneal dialysis, kidney transplantation). *It goes without saying that, in terms of such an approach to treating patients with chronic renal failure, the classification of the syndrome loses practical sense*" (italics of the authors). On the other hand, G.D. Shostka et al. claimed that "the inertia of traditional approaches is too great in Russia, thus making the rejection of the chronic renal failure classification impossible at the moment". At the same time, these authors could not resist the temptation of proposing their own classification of chronic renal failure, whose advantages and disadvantages deserve consideration in another work. Although, according to a famous Russian saying, "a Russian man harnesses horses slowly…" (*which means that it takes a Russian rather long to start doing something – translator note*), Russian medicine has never stayed out of the latest achievements of the world medical science and almost always, after certain adaptation, perceived new principles and approaches. It seems that the process of adopting the CKD definition and classification in Russia will follow the same thorny route. Older doctors remember how long it took today's customary abbreviation of IHD (ischemic heart disease) to be introduced into everyday medical practice. The same can be said about tensions associated with the introduction of the Chronic Obstructive Pulmonary Disease concept in pulmonology.

In our opinion, the NKF classification provides clinicians with clear guidelines (algorithm of actions), which allow the optimal choice of a patient management tactics at each CKD stage. This fully applies to the practice of medical and social expertise departments. The widespread dissemination of the CKD definition and classification is expected to greatly facilitate the work of medical and social expertise specialists.

It is concluded that both the concept of chronic kidney disease and its classification principles can be recommended as suitable for embedment in Russian medical practice.

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